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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,170	WARRELL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006 and 15 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-23 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-23, and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed June 6, 2006 and September 15, 2006.

Claims 2 and 24-28 have been canceled. Claims 1, 4, 5, 13-16, 19, 29, 30, and 32 have been amended.

Claims 1, 3-23, and 29-33 are pending in the instant application.

Claims 1, 3-23, and 29-33 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102 or 35 USC § 103

In the previous Office Action mailed January 25, 2006, claims 1-5 and 13-18 were rejected under 35 U.S.C. 102(b) or 103(a) as being anticipated by or obvious over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141). **This rejection is moot** against claim 2 in view of Applicant's Amendment to cancel claim 2, filed June 6, 2006. **This rejection is withdrawn** against claims 1, 3-5 and 13-18 in view of Applicant's Amendment to the claims, filed June 6, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite that each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide. It is noted that Webb et al. do not teach that each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide.

In the previous Office Action mailed January 25, 2006, claims 1-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986]. **This rejection is moot** against claim 2 in view of Applicant's Amendment to cancel claim 2, filed June 6, 2006. **This rejection is withdrawn** against claims 1 and 3-23 in view of Applicant's Amendment to the claims, filed June 6, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendment to the claims to recite that each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide. It is noted that neither Webb et al., nor Bennett et al. teach or suggest that each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide.

In the previous Office Action mailed January 25, 2006, claims 29-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed January 25, 2006.

Response to Arguments

In response to this rejection, Applicant's argue that neither Webb et al., nor Bennett et al. teach or suggest that each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide. This argument

has been fully considered, but is not found persuasive because the Examiner would like to remind Applicant that claims 29-33 are drawn to a pharmaceutical composition. While the Examiner acknowledges that the claims have been amended to require that each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, this new limitation does not change the properties of the composition, instead, this new limitation appears to be directed for an intended use of the composition. However, since the use of the composition does not require that the composition be any different than what is taught in the combined references of Webb et al. and Bennett et al., the 35 U.S.C. 103(a) rejection is maintained as being unpatentable over Webb et al. in view of Bennett et al.

Applicant's Amendment filed June 6, 2006 necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 13-18, and 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 5, and 13-16 recites the limitations, "The method as in any of Claim 1 or 3" or "The method as in any of Claim 1, 3, or 6". These limitations are grammatically

incorrect since the term, "claim" should be plural because there is more than one claim recited. Recitation of the limitations, "The method as in any of Claims 1 or 3" or "The method as in any of Claims 1, 3, or 6" would obviate in the instant rejection. It is noted that claims 17 and 18 are included in this rejection because of their dependency therein.

Claims 29 and 30 recite the limitation, "said human" in line 4. There is insufficient antecedent basis for this limitation in the claims because neither of the claims ever makes reference to the term, "human". It is noted that claims 31-33 are included in this rejection because of their dependency therein.

Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141, Applicant's reference CP on the Information Disclosure Statement filed February 23, 2001) in view of Waters et al. (Journal of Clinical Oncology, 2000 Vol. 18:1812-1823, Applicant's reference CO on the Information Disclosure Statement filed February 23, 2001).

Claims 1, 3-5, and 13-17 are drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day. Claim 18 is drawn to a specific bcl-2 antisense oligonucleotide comprising SEQ ID NO:17.

Webb et al. disclose bcl-2 antisense therapy at a dose from 4.6 mg/m^2 to 73.6 mg/m^2 in human patients with non-Hodgkin lymphoma (see Abstract). Specifically, Webb et al. disclose the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after a 7 day couse of therapy using a fully phosphorothioated bcl-2 antisense administered to patient 6 (see Figure 2). It is noted that the fully phosphorothioated bcl-2 antisense oligonucleotide disclosed by Webb et al. is 100% identical to SEQ ID NO:17 of the instant invention. Webb et al. are silent regarding the treatment of cancer at day 7 in patient 6. However, since the instant claims are simply drawn to a method of treating cancer in a human comprising one step, namely the administration of a bcl-2

antisense for 3 to 9 days, and Webb et al. disclose the 7-day administration of a bcl-2 antisense oligonucleotide in patient 6 at Figure 2, it is the Examiner's position that at day 7, the cancer in patient 6 was inherently treated since the method disclosed by Webb et al. is fully embraced in the method as instantly claimed.

For further explantation, see MPEP § 2112, which states "[W]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim, but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims".

The Examiner would like to point out that She is not arguing that a reduction in bcl-2 levels is considered to be evidence of cancer treatment. Instead, the Examiner is arguing that since Webb et al. teach the only method step recited in the instant claims, the method disclosed by Webb et al. would inherently "treat cancer", absent evidence to the contrary.

Webb et al. do not teach wherein each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day.

Waters et al. teach interrupted bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma for the purpose of monitoring drug toxicity, treatment efficacy, and response. For example, Waters et al. teach that one course of treatment was planned per patient, but additional courses of treatment were considered in the event of a tumor response (see page 1813, first column). Waters et al. also teach a second course of treatment administered to patients no. 2, 17, and 21, where patient 17 was retreated after 48 hours of his initial course of therapy (see page 1813, first column and page 1818, second column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to devise a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day following the teachings of Webb et al. and Waters et al.

One of ordinary skill in the art would have been motivated to devise a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days since Webb et al. taught the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide. One of ordinary skill in the art would have been motivated to have each cycle of therapy separated by an interval of time wherein the human receives no bcl-2 antisense

oligonucleotide, and wherein said interval of time comprises at least one day since Waters et al. taught bcl-2 antisense oligonucleotide interrupted therapy, for two days, for the purpose of monitoring drug toxicity, treatment efficacy, and response. One of ordinary skill in the art would have been motivated to vary the cycles of therapy or to vary the antisense dosage amount since it is routine and well known in the art to determine optimum dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues as taught by Webb et al.

One of ordinary skill in the art would have expected success at devising a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day since Webb et al. taught the successful use of bcl-2 antisense therapy in a human and Waters et al. taught interrupting the antisense therapy is well tolerated, has no systemic toxicity, and is still effective as a therapeutic.

Therefore the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's filing.

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Claims 1 and 3-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (The Lancet, 1997 Vol. 349:1137-1141, Applicant's reference CP on

the Information Disclosure Statement filed February 23, 2001) in view of Waters et al. (Journal of Clinical Oncology, 2000 Vol. 18:1812-1823, Applicant's reference CO on the Information Disclosure Statement filed February 23, 2001) and Bennett et al. [U.S. Patent No: 6,214,986, made of record in the previous Office Action mailed July 26, 2004].

Claims 1, 3-5, and 13-17 are drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, in combination with a cancer therapeutic agent, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day. Claim 18 is drawn to a specific bcl-2 antisense oligonucleotide comprising SEQ ID NO:17. Claims 6-12 and 19-23 are drawn to a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, in combination with a cancer therapeutic agent, wherein each cycle of therapy is separated by an interval of time wherein said human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day.

Webb et al. and Waters et al. are relied upon as taught in the 35 U.S.C. 103(a) rejection above against claims 1, 3-5, and 13-18.

Neither Webb et al. nor Waters et al. teach further administering the antisense oligonucleotide with one or more cancer therapeutics and at specific doses.

Bennett et al. teach the antisense modulation of bcl expression using therapeutic compositions comprising antisense oligonucleotides. Bennett et al. also teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics that function by a non-antisense mechanism, including doxorubicin, 5-fluorouracil (5-FU), etoposide, and cisplatin, for example (see column 16, lines 28-52). Bennett et al. teach "the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16-17, last and first paragraphs, respectively).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to devise a method of treating cancer in a human

comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, wherein each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day using the teachings of Webb et al. and Waters et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the antisense therapy further comprising administering one or more cancer therapeutics using the teachings of Bennett et al.

One of ordinary skill in the art would have been motivated to devise a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days since Webb et al. taught the reduction of bcl-2 protein levels in the lymph node aspirates of patient 6 after the 7-day administration of a fully phosphorothioated bcl-2 antisense oligonucleotide. One of ordinary skill in the art would have been motivated to have each cycle of therapy separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day since Waters et al. taught bcl-2 antisense oligonucleotide interrupted therapy, for two days, for the purpose of monitoring drug toxicity, treatment efficacy, and response. One skilled in the art would have been motivated to administer the antisense therapy further comprising administering one or more cancer therapeutics or chemoagents as taught by Bennett et al. since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment. One of ordinary skill in the art would have

been motivated to vary the cycles of therapy or to vary the antisense dosage amount since it is routine and well known in the art to determine optimum dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues as taught by either Webb et al. or Bennett et al.

One of ordinary skill in the art would have expected success at devising a method of treating cancer in a human comprising administering a bcl-2 antisense in one or more cycles of therapy, each cycle of therapy consisting of 3 to 9 days, and wherein each cycle of therapy is separated by an interval of time wherein the human receives no bcl-2 antisense oligonucleotide, and wherein said interval of time comprises at least one day since Webb et al. taught the successful use of bcl-2 antisense therapy in a human and Waters et al. taught interrupting the antisense therapy is well tolerated, has no systemic toxicity, and is still effective as a therapeutic. One of ordinary skill in the art would have expected success at administering the antisense therapy further comprising administering one or more cancer therapeutics or since Bennett et al. taught how to successfully use antisense compounds with one or more other chemotherapeutic agents which function by a non-antisense mechanism.

Therefore the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's filing.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
November 21, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635